Case Report

Rare Case of Fatal Yellow Fever Vaccine-associated Viscerotropic Disease

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Abstract: This report describes a case of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) that occurred after vaccination in a 22-year-old female. Our patient presented with a clinical syndrome of fever, headache, nausea, and vomiting, which quickly progressed to multiorgan failure and ultimately death on hospital day 4. YEL-AVD is an extremely rare condition reported only a few times in the literature. The yellow fever vaccine is a known stimulus of systemic inflammation in the body. A mild subclinical viremia develops, which results in a persistent and robust T-helper-cell-dependent antibody response with long-lasting immune protection. The very rare patient may have an aberrant response to the 17D vaccine strain, causing the multiple organ system failure seen in YEL-AVD. Predisposing host factors that contribute to YEL-AVD are not yet known. Treatment for YEL-AVD is supportive. To the authors' knowledge, this patient was the first to have YEL-AVD as a result of standard US military vaccination protocols.

Key Words: multiorgan system failure, yellow fever vaccine-associated viscerotropic disease

Yellow fever is a mosquito-borne disease, caused by an RNA virus of the genus *Flavivirus*, family *Flaviviridae*. It is endemic in most of sub-Saharan Africa and tropical South America, with more than 90% of the cases occurring in Africa. There are approximately 200,000 cases per year. The virus replicates in the tissues local to the site of inoculation and in localized lymph nodes. It then spreads to the liver, spleen, bone marrow, and myocardium. The quiescent incubation period usually lasts 3 to 6 days, and then fever, myalgias, headache, and emesis develop. Most patients will improve after 3 to 4 days, but approximately 15% enter a "toxic phase," characterized by disseminated intravascular coagulation (DIC) with persistent fevers and hemolytic jaundice. Half of the patients who enter the toxic phase die within 2 weeks. Those who recover usually do so without significant lasting organ damage.[1]

The live, attenuated 17D vaccine against yellow fever has been used effectively as a vaccine for more than 50 years. Yellow fever was the third human disease to be controlled by vaccination, after smallpox and rabies.[2] Currently, the yellow fever vaccine is manufactured by six World Health Organization-approved institutes worldwide.[2] The yellow fever vaccine is used as a routine immunization for infants in many countries, and a valid certificate of vaccination is required for travelers to enter 127 countries worldwide.[3]

The 17D vaccine is thought to be a safe, preventative therapy against the development of yellow fever in patients at risk for the disease. However, a very small number of patients can have an atypical response to the vaccine, which, as in our patient, can result in death.

Case Report

A 22-year-old female presented to the Emergency Department with a 4-day history of vomiting and 3 days of diarrhea. She had up to 15 episodes of emesis per day

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Key Points

- Disseminated yellow fever infection can occur from yellow fever vaccine, though predisposing host factors are not known.
- Yellow fever vaccine-associated viscerotropic disease must be considered in any patient with multiorgan system failure occurring several days after receiving the yellow fever vaccine.
- Treatment for yellow fever vaccine-associated viscerotropic disease, like treatment for wild-type yellow fever virus infection, is largely supportive at this time.
- In areas endemic with yellow fever, the vaccine remains the most effective prevention against the disease.

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for the past 4 days, which occurred about 10 minutes after eating. She had four to five nonbloody, liquid stools per day. She was active duty in the Air Force and had presented to the troop medical clinic 2 days before presentation with similar complaints. She was treated with fluids and empiric amoxicillin. There was no interval improvement in her symptoms.

Her medical history was significant for occasional migraine headaches. She was a nonsmoker and reported occasional alcohol use. She was of Pacific Islander ancestry. She was single but sexually active with one male partner. She had no recent travel, sick contacts, new sexual contacts, or dietary changes. Six days before her presentation, she had received a yellow fever vaccine (Connaught, lot number UO253AA) and an influenza vaccine (Aventis Pasteur, lot number UO983AA) per standard protocol in preparation for an upcoming deployment. At the time of admission, she was unsure which vaccines she had received.

In the Emergency Department, an oral temperature measured 104.1°F. Her blood pressure was 110/56 mm Hg, heart rate was 110 beats per minute, and respirations were 16 per minute. Her examination was significant for photophobia with nuchal rigidity, along with dry mucous membranes. The cardiopulmonary examination was significant only for a regular tachycardia. Her abdomen showed mild epigastric tenderness to palpation but was otherwise unremarkable. A detailed neurologic examination was normal.

Initial laboratory studies were performed. Her white blood cell count was 3,100/mm^3, with a left shift of 93% neutrophils (along with 39% bands) and an absolute lymphocyte count of only 200/mm^3. Hemoglobin and platelets were normal. Her initial liver-associated enzymes were aspartate aminotransferase of 111 IU/L, alanine aminotransferase of 72 IU/L, γ-glutamyltransferase of 117 IU/L, and alkaline phosphatase of 94 IU/L. Albumin was 2.4 g/dL, and total bilirubin was 1.1 mg/dL. Coagulation studies were normal. Serum chemistries were significant for sodium of 131 mmol/L, potassium of 3.3 mmol/L, magnesium of 1.4 mg/dL, and phosphorous of 1.3 mg/dL. The human immunodeficiency virus enzyme-linked immunosorbent assay was negative.

Lumbar puncture was performed. The cerebrospinal fluid (CSF) glucose was 72 mg/dL and the protein was 60 mg/dL. The fluid was clear and colorless. CSF Gram stain showed no organisms and less than 5 white blood cells per high-power field. The latex agglutination panel was negative. Stool studies were sent, which were positive for fecal leukocytes but negative for *Clostridium difficile* or ova and parasites. Stool culture was also negative.

Radiologic studies included a right upper quadrant ultrasound. It showed a single stone in the gallbladder and a small amount of pericholecystic fluid but no ductal dilation.

She was admitted to the ward for supportive care and was treated with empiric ampicillin/sulbactam for a suspected gastrointestinal infection. Despite aggressive fluid resuscitation, she remained hypotensive with persistent fevers greater than 102°F. The aspartate aminotransferase and alanine aminotransferase levels rose to 238 IU/L and 110 IU/L, respectively, and she had development of mild DIC, with low fibrinogen, high fibrin split products, and high D-dimer. She was transferred to the intensive care unit, and pulmonary artery catheterization showed distributive shock. She had development of respiratory failure and required intubation. Given our lack of a definite identified source of infection and her rapid decline, the antibiotics were broadened to ticarcillin/clavulanate, clindamycin, doxycycline, fluconazole, and acyclovir. On hospital day 3, a contrast computed tomography of the abdomen showed mild mesenteric fat stranding with mild thickening in the distal ileum and cecum. Her WBC at that time rose to above 20,000/mm^3, and blood, CSF, and urine cultures remained negative. She was taken for emergent exploratory laparotomy to assess for an intra-abdominal source of sepsis. The laparotomy showed a dilated right colon with clear ascitic fluid. A hemicolectomy and excision of a prominent mesenteric lymph node was performed. One hour after surgery, on hospital day 4, she had a ventricular fibrillation cardiac arrest and died, despite aggressive advanced cardiac life support measures.

The cause of her systemic inflammatory response syndrome and rapid clinical deterioration was initially unclear. An autopsy was performed, and liver, kidney, brain, heart, adrenals, lymph nodes, and bone marrow specimens were sent to the Armed Forces Institute of Pathology (Washington, DC) and the Centers for Disease Control (CDC, Atlanta, GA) for review. Physical findings on autopsy included gross hepatomegaly with a yellowish discoloration and splenomegaly. There was evidence of widespread dissemination of yellow fever viral antigen as well as active viral replication in multiple organs including the liver, lungs, brain, heart, spleen, kidney, and lymph nodes. This distribution of viral antigen differs from fatal wild-type yellow fever virus infection. According to the CDC, with wild-type infection, viral antigens are never seen outside the liver.* Electron microscopy of the spleen and lung tissues showed cellular foci of smooth-membrane vesicles consistent with flavivirus replication complexes. Subsequent immunogold labeling using anti-yellow fever virus antibody confirmed the viral nature of these complexes.

*Private correspondence from the Centers for Disease Control concerning the patient's autopsy findings.

Discussion

Case reports of adverse reactions to the yellow fever vaccine have been known for some time. In 1941, 199 cases of encephalitis occurred after vaccination with an early 17DD vaccine in Brazil after administration of more than 55,000 doses of the vaccine.[4] None were known to be fatal. After this outbreak, the technique of the 17D yellow fever vaccine production was refined with the introduction of a seed-lot system. After this refinement, during the period between 1942 and 1966, more than 100 million doses of the 17D vaccine were distributed, with only 15 severe adverse events (all encephalitis) reported. All these events were in infants younger than 7 months old, and all recovered. The first known fatality to be associated with the millions of distributed doses since 1942 was in 1965, in a 3-year-old girl who died as a result of acute encephalitis after receiving the vaccine.[4]

In recent years, cases of multiorgan system failure in recipients of the 17D vaccine have been reported. Between 1996 and 2001, for example, five persons ages 56 to 79 became ill between 2 and 5 days after receiving the vaccine in anticipation of international travel (four Americans and one Australian). Two younger Brazilians, ages 5 and 22 years, were affected after receiving the vaccine in 1999 and 2000 as part of a campaign to control a local yellow fever epidemic.[5] These patients all had prodromes and multiorgan system failure similar to our patient, and six of the seven died. The survivor, a 76-year-old man, was successfully treated with supportive care and discharged from the hospital 22 days after admission.[6]

Previously called multiorgan system failure, this syndrome is now called yellow fever vaccine-associated viscerotropic disease (YEL-AVD). There is a related postvaccination syndrome that affects the nervous system, previously called postvaccinial encephalitis and now called yellow fever vaccine-associated neurotropic disease (YEL-AND).[7] One recent publication noted only 13 reported cases of YEL-AVD out of more than 100 million doses of the vaccine given worldwide.[8]

The yellow fever vaccine is known to stimulate the immune system and cause an inflammatory response. It causes a reproducible increase in the plasma concentrations of tumor necrosis factor-α, a cytokine that is crucial in the regulation of the immune response and inflammation.[9] Van der Beek et al[10] noticed a significant increase in interleukin-6, C-reactive protein, and fibrinogen levels occurring after vaccination. Importantly, they noticed that the time course of the inflammatory response correlated with the occurrence of viremia, which typically occurs 4 to 6 days after vaccination.[10] We did not measure inflammatory cytokines or the degree of viremia in our patient during her rapid clinical deterioration.

It is known that the 17D yellow fever vaccine causes, in most cases, a subclinical viremia.[2] This viremia is needed to activate the cellular immune system to induce the antibody response (through the $CD4^+$ T-cells). In the vast majority of patients who receive the vaccine, there is very limited viral replication that occurs in the host but a very strong and persistent antibody response, protecting the host for years against contracting the disease.[11] In one study, no significant changes in inflammatory markers were noticed in patients who received a second vaccine after having first received a yellow fever vaccine at least 10 years prior.[12]

Patients who have development of YEL-AVD after vaccination do so because of a widespread inflammatory response, an atypical host response to the vaccine strain. Why a very small percentage of patients have YEL-AVD is still not clear. No data exist that support immunodeficiency as a predisposing factor to severe or fatal reactions to the vaccine; indeed, no reported cases of YEL-AVD have occurred in immunocompromised patients.[13]

Galler et al[14] analyzed yellow fever vaccine viruses that were associated with serious adverse outcomes in patients in Brazil. They found that the fatal adverse events were not due to genetic factors intrinsic to the viruses but rather were most likely secondary to individual host factors that control cellular susceptibility to yellow fever viruses. Likewise, a large variation in the acute phase response to yellow fever vaccination has been found among recipients, even classifying patients as hyperresponders or hyporesponders.[15] The response of an individual patient to the vaccine is thought to be genetically determined.[15] Unfortunately, the specific host factors that might put a patient at risk for development of YEL-AVD are not yet known and represent an important area of research for the future. The CDC web site indicates that further investigation into this area is ongoing.[16]

Similar to the treatment for wild-type yellow fever virus infection, the treatment for YEL-AVD is largely supportive. It is recommended that any patient who has an undiagnosed febrile illness within 10 days after vaccination be investigated and hospitalized if the liver enzymes are elevated. Serial blood samples for quantification of viremia and antibody analysis need to be sent, and frozen buffy coat cells should be kept for future genetic analysis.[17] Patients will often need to be placed in the intensive care unit for treatment of hemorrhage, shock, and hepatic failure. Nasogastric suctioning and histamine-2 receptor blockers have been helpful in reducing the risk of bleeding.[18]

In patients who have been exposed to yellow fever, hyperimmune globulin therapy is useful for postexposure prophylaxis, but it is of no benefit after the clinical syndrome begins.[19] It appears that its utility in treating YEL-AVD would be very limited, since patients would not generally present until after the start of the clinical syndrome. In addition, interferon-γ has shown some therapeutic benefit in delaying organ failure and death, though it did not show any effect on overall mortality rates.[20] Concerning antiviral therapy, ribavirin is known to be of benefit in treating *Lassa* virus (an arenavirus) hemorrhagic fever, but it has not yet been proven

to be of benefit in treating yellow fever.[18] Despite showing activity in vitro at high concentrations, it was not shown to be useful during preclinical studies in monkeys.[19] Any YEL-AVD event also needs to be reported to the Vaccine Adverse Events Reporting System (VAERS, 1–800–822–7967). In the reported cases of YEL-AVD, only a few had a medical history that was known to be more extensive than that of our 22-year-old female. One case involved a 76-year-old male with known chronic renal insufficiency and Crohn disease.[6] In another case, the 79-year-old female had known hypothyroidism, hypertension, and polymyalgia rheumatica (but without steroid use for 6 months before receiving the vaccine).[6] Other patients, like ours, were well, with only minor chronic medical problems (such as chronic low back pain in a 56-year-old male).[21] None had known immunodeficiency, and all were in their usual state of health before receiving the vaccine. Our patient was by all accounts in excellent health at the time she received the vaccine.

Similar to our patient, the initial presenting syndromes of YEL-AVD are characterized by fever, headaches, nausea, vomiting, and myalgias, followed by respiratory failure. Lymphocytopenia, as in our patient, is common, as is moderate elevation in the hepatocellular enzymes.[13]

Conclusion

Yellow fever continues to be a significant cause of morbidity and mortality in certain regions across the world. Although cases such as ours representing YEL-AVD and its neurologic counterpart, YEL-AND, can occur and are reported, they continue to be extremely rare, relative to the amount of yellow fever vaccine given worldwide. Yellow fever vaccine is still recommended when travel to endemic areas is anticipated. Our case represents, to our knowledge, the first case of YEL-AVD that occurred as a result of standard US military vaccination procedures.

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